PATENT
2121-0128P

IN THE U.S. PATENT AND TRADEMARK OFFICE

In re application of:		Before the Board of Appeals	
Georges BAHR		Appeal No.:	
Appl. No.:	08/809,650	Group:	1648
Filed:	June 13, 1997	Examiner:	L. Scheiner
Conf.:	7849		
For:	COMPOSITIONS OF MURAMYL PEPTIDES INHIBITING THE REPLICATION OF HIV		

BRIEF FOR THE APPELLANT UNDER 37 C.F.R. §1.192

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Assistant Commissioner for Patents
Washington, DC 20231

March 18, 2003

Sir:

The present brief for the Appellant is submitted pursuant to 37 C.F.R. 1.192.

I) Real Party in Interest

The real party in interest in the present application is Vacsyn, S.A. of Paris, France, as evidenced by the assignment recorded at Reel/Frame 8740/0343.

II) Related Appeals and Interferences

There are no related appeals or interferences.

III) Status of Claims

Claims 14-34 were filed with the application and new claims 35-40 were added during prosecution. Claims 14-24 and 35-40 have been cancelled. Thus, claims 25, 26 and 28-34 stand on appeal.

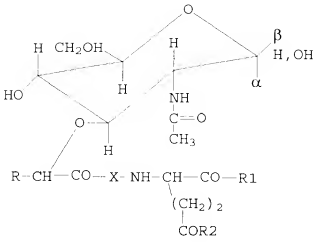
IV) Status of Amendments

The amendment filed on February 19, 2002 has been entered. The amendment filed on July 18, 2002 has been entered. In the Notification of Non-Compliance issued on November 5, 2002, the Examiner stated that a statement of the status of any amendments filed subsequent to final rejection had note been included. However, the Appeal Brief filed on July 18, 2002 did, in fact, include a complete statement of the status of the amendments filed after final rejection, which statement has been repeated and updated herein. If for some reason the Examiner still believes the present statement is insufficient, she is requested to contact the undersigned.

Appellants further note that in Item 8 of the Notification of Non-Compliance, the Examiner indicates that the Brief does not contain a correct current copy of the appealed claims. Appellants note the typographical error in claim 26 (improperly numbered as claim 25). The attached claim appendix corrects this error. In addition, claim 34 was truncated in the electronic version of the specification provided on July 26, 2001. However, the correct version of claim 34 was examined in the Office Actions and the correct version of claim 34 was attached to the previous Appeal Brief. As such, the error in the electronic version of claim 34 is believed to have been a harmless error.

V) Summary of Invention

The present invention is most broadly directed to a process for inhibiting the replication of acquired immunodeficiency retroviruses, by administering as a principal ingredient an effective amount of a muramyl peptide of formula:



in which the group R is a methyl group; X is an L-alanyl residue, and R1 is an $O(CH_2)_xH$ group with x= 1, 2, 3 or 4, R2 is, independently of R1, either an amino or an $O(CH_2)_xH$ group with x= 1, 2, 3 or 4 (See page 4, lines 1-6 of the specification), wherein the effective amount is also an amount that is capable of causing a 100% inhibition of the replication of said retroviruses in primary cultures of monocytes of the host (See page 5, lines 17-24 of the specification).

The present invention is further drawn processes using subgenera and specific species of the above formula, processes using the muramyl peptide in combination with another molecule capable of enhancing the anti-retroviral action of the peptide (See page 7, lines 22-28 of the specification), and to processes of treating or preventing specific diseases (See page 7, lines 17-21 of the specification).

VI) Issues on appeal

1) The first issue on appeal is whether Schreck et al. discloses every limitation of the invention of claims 25, 26, 28-30 and 34 so as to anticipate the invention under 35 U.S.C. §102(b).

2) The second issue on appeal is whether Masihi et al. discloses every limitation of the invention of claims 25, 26, 28-30 and 34 so as to anticipate the invention under 35 U.S.C. §102(b).

3) The third issue on appeal is whether Masihi et al. suggests the invention of claims 31-33 so as to render the invention obvious under 35 U.S.C. §103(a).

VII) Grouping of the claims

For purposes of appeal, the claims are grouped and will be argued as follows.

Group I - Claims 25, 28-29 and 34

Group II - Claims 26 and 30

Group III - Claims 31-33

VIII) Arguments

Group I - Claims 25, 28-29 and 34

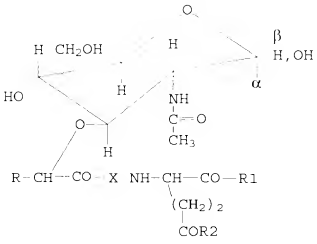
Issue 1 - whether Schreck et al. discloses every limitation of the invention of claims 25, 28-29 and 34 so as to anticipate the invention under 35 U.S.C. §102(b).

Claims 25, 28-29 and 34 have been rejected under 35 U.S.C. §102(b) as being anticipated by Schreck et al. The Examiner asserts that Schreck et al. discloses the administration of murabutide, both *in vitro* and *in vivo*, and finds that the apyrogenic molecule induced either low activation levels or no activation of (NF-κB).

"To anticipate a claim, a prior art reference must disclose every limitation of the claimed invention, either explicitly or inherently." In re Schreiber, 128 F.3d 1473, 1477, 44 USPQ2d 1429, 1431 (Fed. Cir. 1997). In addition, to support a rejection for anticipation the Examiner must completely identify each and every facet of the invention. Ex parte Levy 17 USPQ2d 146 (Bd. Pat. App. & Interfer. 1990).

The present invention of claims 25, 28-29 and 34 is drawn to a process for inhibiting the replication of acquired immunodeficiency retroviruses, by administering as

a principal ingredient an effective amount of a muramyl peptide of formula:



wherein the effective amount is also an amount that is capable of causing a 100% inhibition of the replication of said retroviruses in primary cultures of monocytes of the host.

There is no disclosure or suggestion in Schreck et al. that muramyl peptides can inhibit the replication of immundeficiency retroviruses. Rather, Schreck et al. teach the use of muramyl peptides as adjuvants in AIDS vaccines. Schreck et al. do not teach any specific inhibitory activity on the replication of acquired immunodeficiency retroviruses for any of the muramyl peptides assayed. Indeed throughout the experimental section of this publication no HIV-1 infected cells were used. Rather three types of cells lines were used which were human Jurket T cells, a human monocyte-macrophage cell line

called Mono-Mac-8 and a mouse pre-B cell line 70Z/3.12. As indicated in the Material and Methods section, none of these cell lines were infected with HIV-1. Thus, with Schreck et al. the compounds were never exposed to HIV-1 and it was not possible to achieve the invention with Schreck et al., either explicitly or inherently.

In response to the above argument, the Examiner has contended that the method of the invention does not exclude methods of prophylaxis and thus also encompasses treatment of non-infected cells. While Appellants do not disagree with this contention, the Examiner still has not put forth on the record the particular part of Schreck et al. that discloses, either explicitly or inherently, that by administering their disclosed muramyl peptides inhibition of immunodeficiency retroviruses can be achieved.

Indeed, the experiments in Schreck et al. only teach the skilled artisan that there is no inducible activation of NG-kB in various cell lines when MDP-(DD), murabutide or MDP(thr)-GDP were tested. An absence of activation of NF-kB cannot be equaled with inhibition of HIV replication or HIV viral suppression.

The biological definition and plain meaning of "inhibition" means to decrease, limit or block the action

or function. Claims 25, 28-29 and 34 recite the inhibition of immunodeficiency retrovirus replication.

In contrast, a general biological definition of "activation" means to convert certain biological compounds into biological derivatives. Thus, in Schreck et al., when the cellular transcription factor NF-kB is "activated," it binds to two motifs in the HIV-1 LTR and consequently activates the LTR driven RNA transcription, hence increasing HIV-1 replication. When the NF-kB is not activated it remains "dormant" and thus does not lead to an increase in HIV-1 replication.

It was never demonstrated in Schreck et al. that any of the muramyl peptides inhibited NF-kB activation and hence might be linked to HIV-1 inhibition. Furthermore, it is well known that process claims are known to be a means or a method to achieve or produce a result. See Coming v. Burden, 56 U.S. (15 How 267 1853). The result achieved by the presently claimed invention is that of inhibiting the replication of immunodeficiency retroviruses. This result is achieved by administering the muramyl peptides of the present invention.

It cannot be said that Schreck et al. demonstrates that the disclosed muramyl peptides possess HIV inhibitory

activity or that the peptides in Schreck et al. teach the invention of claims 25, 28-29 and 34.

Moreover, as stated by the Federal Circuit in Lindeman Maschinefabrik GMBH v. American Hoist and Derrick Co., 730 F2d 1452, 1458 (Fed. Cir. 1984):

> Further, the reference must be sufficiently clear so as to prove the existence of each and every element in the reference.

Appellants contend that the rejection under 35 U.S.C. § 102(b) cannot be maintained since the major elements of the claims on Appeal are not set forth in this publication, either explicitly or inherently.

The elements of claims 25, 28-29 and 34 recite the administration of an effective amount of a particular genus of muramyl peptides as a principal ingredient to inhibit immunodeficiency retroviruses. The effective amount muramyl peptide is capable of causing a 100% inhibition of replication of the retrovirus in primary cultures of monocytes of the host.

Schreck et al. fail to disclose administering the muramyl peptides disclosed therein as a principal ingredient. Appellants strongly contend that a principal ingredient cannot be interpreted to mean an adjuvant.

An "adjuvant" is a material used in conjunction with highly purified vaccines made from small molecular weight

antigens, which are poor immunogens. These vaccines are poor immunogens because they lack intrinsic adjuvanicity that is usually provided by more complex natural and higher molecular weight molecules. Thus, T cell epitopes that elicit help for antibody production against the B cell epitope reside on the "adjuvant portion" of the antigen molecule and without the adjuvant portion the antigen produces a lower level of immunity. In addition, adjuvants help to provide the appropriate physical structure to the antigen so that the epitope is identified and processed by the immune system to generate an immune response. An adjuvant is a material that makes the target antigen more immunogenic to the immune system and thus helps elicit a stronger immune response to the antigen (principal ingredient).

Thus, an adjuvant cannot be considered as a principal ingredient in a vaccine, since it is the antigen *per se* that is foremost in importance in a vaccine to obtain immunity and not the adjuvant. It should be emphasized that importance is not a measure of quantity, but effect.

Thus, administering muramyl peptides as a principal ingredient is not disclosed in Schreck et al.

In addition, Schreck et al. fails to teach or disclose administering an effective amount of the claimed muramyl

peptides of the claims 25, 28-29 and 34, wherein the effective amount is an amount that is capable of causing a 100% inhibition of the replication of said retroviruses in primary cultures of monocytes of the host. This feature is not explicitly disclosed in Schreck et al. Nor can it be inherently inferred to the reference, since as discussed above, Schreck et al. do not disclose that their muramyl peptides can inhibit the replication of immunodeficiency retroviruses, nor did they ever expose HIV-1 to the peptides.

Therefore, Appellants submit that with respect to Claims 25, 28-29 and 34, Schreck et al. cannot be said to anticipate these claims, either explicitly or inherently.

Of concern to the Appellants is the fact that the Examiner appears to have maintained this rejection based on an "inherent disclosure." However, the Examiner has not clearly indicated in the record that the basis of the rejection is one of inherency; i.e. the Examiner never explicitly brought up this issue in any Official Action.

Moreover, if the rejection is based on inherency, the Examiner has not met her burden required by law as set forth in *In re Levy, supra*, where the Board of Patent Appeals and Interferences stated the following:

> In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the prior art.

Even if the Examiner asserts the inherency principle with respect to anticipation of the claims, although it is not of record, Appellants maintain that claims 25, 28-30 and 34 are not even inherently anticipated by Schreck et al.

The mere fact that Schreck et al. teach in the Discussion section that muramyl peptides have been utilized as adjuvants in experimental vaccines against SIV and HIV does not disclose that these vaccines were capable of inhibiting immunodeficiency retrovirus replication. In fact, the authors only mentioned with respect to these vaccines that they have "promising activities." What "promising activities" means is certainly not clear and leaves a multitude of doubts.

The Examiner jumps to the erroneous conclusion that the Discussion section in Schreck et al. teaches a vaccine in which muramyl peptides were used and hence this vaccine when administered must inhibit immunodeficiency retrovirus replication. This is clearly not explicitly stated and cannot be implicitly implied, since as of this date,

Appellants are not aware of any successful vaccine to treat HIV or SIV. Thus, successful inhibition of an immunodeficiency retrovirus replication has not yet been demonstrated, since a vaccine at the very least would require such inhibition for prophylaxis purposes.

In fact, eight (8) years after the publication of Schreck et al., as evidenced in Appendix II ("Why don't we have one yet?") there still was no successful HIV vaccine.

To maintain a 35 U.S.C. § 102(b) rejection based on inherent anticipation requires more than assumptions read into the prior art. Rather, there must be a clear disclosure, which is not based on mere promising results. This interpretation is clear as evidence by Federal Circuit in *In re Robertson*, 169 F3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) where the Court stated:

> Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.

The fact that Schreck et al. disclose that the vaccine using muramyl peptides had promising activities could not lead one to conclude that the muramyl peptides in this vaccine lead to inhibiting the immunodeficiency retrovirus replication. Nor can it be concluded that the effective amounts administered were such that the muramyl peptides

were capable of causing a 100% inhibition of the replication of said retroviruses in primary cultures of monocytes of the host.

Thus, it can only be concluded that claims 25, 28-29 and 34 are not anticipated either explicitly or inherently by Schreck et al.

Issue 2 - whether Masihi et al. discloses every limitation of the invention of claims 25, 28-29 and 34 so as to anticipate the invention under 35 U.S.C. §102(b).

Contrary to the assertion of the Examiner, the invention of Claims 25, 28-29, and 34 satisfies the requirement of novelty of 35 U.S.C. § 102(b), in view of Masihi et al. because Masihi et al. fail to disclose that the murabutide used in the reference as an adjuvant inhibits immunodeficiency retrovirus replication in man and further fails to disclose what effective amount should be administered.

The Examiner contends that Masihi et al. anticipate claims 25, 28-29, and 34 under 35 U.S.C. § 102(b). Appellants submit that the rejection is not sustainable.

Appellants also submit that for very similar reasons discussed above regarding Schreck et al., claims 25, 28-29,

and 34 are not anticipated by Masihi et al. The arguments made regarding the rejection over Schreck et al. equally apply to Masihi et al. and these arguments are therefore incorporated herein by reference in order to avoid repetitiveness.

Essentially, the Examiner asserts that since a single sentence in Masihi et al. teach that murabutide was used as an adjuvant in human clinical trials for AIDS, that claims 25, 28-29 and 34 are anticipated by this reference.

It should be specifically stated that the sole reliance by the Examiner in maintaining this rejection appears at page 397 of Masihi et al. where the following is stated:

> A nonpyrogenic butyl ester analog of MDP, murabutide, has been used as an adjuvant in human clinical trials.

First of all, it should be stressed that an adjuvant is not considered by those skilled in this art as a principal ingredient. This is not a question of semantics, as the Examiner purports, but a question of scientific terminology. See the relevant discussion in the argument regarding Schreck et al. as to the difference between an "adjuvant" and a "principal ingredient." Again, by definition, an adjuvant is a substance which, when used in

combination with a specific antigen produces a higher level of immunity than that produced by the antigen alone.

Therefore, an adjuvant cannot be considered as a principal ingredient in a vaccine, since it is the antigen *per se* that is foremost in importance in a vaccine to obtain immunity and not the adjuvant. It should be emphasized that importance is not a measure of quantity but effect.

Moreover, like Schreck et al., Masihi et al. is completely silent with respect to the results obtained from the AIDS trial. The mere statement that murabutide has been administered to a human does not imply that it has been used with success, such that HIV-1 replication was inhibited. It cannot be assumed or inferred from this sole sentence in Masihi et al. that inhibition of immunodeficiency retrovirus replication was in fact achieved.

The Supreme Court clearly stated in Eibel v Minnesota & Ontario Paper Co., "accidental results, not intended and not appreciated, do not constitute anticipation." Eibel Processing Co. v. Minnesota & Ontario Paper Co. 261 U.S. 45 (1923). The Federal Circuit stated in In re Roberton that, "to establish inherency...extrinsic evidence must make clear that the missing descriptive matter is necessarily

present in the thing described in the reference *and it would be so recognized by persons of ordinary skill."* (emphasis added) In re Roberston 49 U.S.P.Q.2d 1949 (Fed. Cir. 1999) similarly in Rosco v. Mirror Lite, the Federal Circuit held that for anticipation by inherency one skilled in the art must "read" the reference as disclosing the invention. Rosco v. Mirror Lite Co., 64 USPQ2d 1676 (Fed. Cir. 2002).

There is no way that one skilled in the art would ever read the one sentence disclosure in Masihi et al. that MDP was used as an adjuvant as inherently disclosing that an effective amount of the muramyl peptides of claim 1 were administered to a patient to inhibit the replication of immunodeficiency virus and that the amount of muramyl peptide administered was sufficient to result in 100% inhibition of HIV in primary cultures of monocytes of the host. As such, the threshold and showing for a rejection by inherency has not been met.

Therefore, each and every element of Claims 25, 28-29 and 34 are neither explicitly nor inherently disclosed in Masihi et al. and the rejection of the these claims as being anticipated by Masihi et al. must be withdrawn.

Group II - Claims 26 and 30

Issue 1 - whether Schreck et al. discloses every limitation of the invention of claims 26 and 30 so as to anticipate the invention under 35 U.S.C. §102(b).

The invention of claim 26 is drawn to the very narrow subgenus of compounds wherein R1 and R2 are $O(CH_2)_xH$ groups. The invention of claim 30 recites the feature that the muramyl peptide is administered together with another molecule capable of enhancing the anti-retroviral action of the muramyl peptide. The arguments presented above under Group I, Issue 1), regarding the patentability of the invention of claims 25, 28-29 and 34 over Schreck et al. are equally applicable to claims 26 and 30, which depend from claim 25, and are hereby incorporated by reference for the sake of brevity. However, the inventions of claims 26 and 30 are separately patentable from claims 25, 28-29 and 34, over Schreck et al. for the reasons that follow.

As noted above, the invention of claim 26 requires the administration of muramyl peptides wherein R1 and R2 are $O(CH_2)_xH$ groups. There is no disclosure in the Schreck et al. of the muramyl peptides of claim 26. As such, Schreck et al. fails to disclose each and every feature of claim 26

and Schreck et al. fails to anticipate the invention of claim 26.

Likewise for claim 30 there is no disclosure in Schreck, et al. of the feature of administering another compound capable of enhancing the anti-retroviral action of the muramyl peptide with the muramyl compositions of the invention, as set forth in claim 30. As such, Schreck et al. fails to disclose each and every feature of claim 30 and Schreck et al. fails to anticipate the invention of claim 30.

Issue 2 - whether Masihi et al. discloses every limitation of the invention of claims 26 and 30 so as to anticipate the invention under 35 U.S.C. §102(b).

The arguments presented above under Group I, Issue 2), regarding the patentability of the invention of claims 25, 28-29 and 34 over Masihi et al. are equally applicable to claims 26 and 30, which depend from claim 25, and are hereby incorporated by reference for the sake of brevity. In addition, the inventions of claims 26 and 30 are separately patentable from claims 25, 28-29 and 34, over Masihi et al. for the reasons that follow.

As noted above, the invention of claim 26 requires the administration of muramyl peptides wherein R1 and R2 are

$O(CH_2)_xH$ groups. There is no disclosure in the Masihi et al. of the muramyl peptides of claim 26. As such, Masihi et al. fails to disclose each and every feature of claim 26 and Masihi et al. fails to anticipate the invention of claim 26.

Likewise for claim 30 there is no disclosure in Masihi et al. of the feature of administering another compound capable of enhancing the anti-retroviral action of the muramyl peptide with the muramyl compositions of the invention, as set forth in claim 30. As such, Masihi et al. fails to disclose each and every feature of claim 30 and Masihi et al. fails to anticipate the invention of claim 30.

Group III- Claims 31-33

Issue 3) - whether Masihi et al. suggests the invention of claims 31-33 so as to render the invention obvious under 35 U.S.C. §103(a).

The invention of claims 31-33 satisfies the requirement of nonobviousness, as defined by 35 U.S.C. §103(a), in view of Masihi et al. The Examiner deems that claims 31-33 are obvious in view of Masihi et al. The Examiner asserts that

> Masihi teach the use of human recombinant GM-CSF in combination with zidovudine for treatment of AIDS in humans and, it would have been obvious to one of ordinary skill in the art at the time of the invention to have administered the murabutide in combination with another molecule such as a cytokine, GM-CSF or a protease inhibitor since said respective molecules are well known to be effective in the treatment of AIDS.

However, the Examiner's conclusion of the obviousness of claims 31-33 is improper for the following reasons.

Firstly, Masihi et al. does not disclose combinations of cytokines or protease inhibitors with an HIV-1 inhibitor.

Claim 31 and claim 33 recite that specific molecules such as cytokines and protease inhibitors are used to enhance the retroviral activity of the muramyl peptides. These specific molecules are not disclosed or even suggested within the four corners of Masihi et al. Nor is there any prior art of record that teaches or suggests combining a muramyl peptide with cytokines or protease inhibitors.

As stated in *In re Burt and Walter*, 148USPQ 549(CCPA 1966):

> [S]ilence in a reference is not a proper substitute for an adequate disclosure of facts from which a conclusion of obviousness may justifiably follow.

Therefore, Appellants submit that without any disclosure of the combination of cytokines or protease inhibitors with a muramyl peptide as presently claimed, this rejection with respect to Claims 31 and 33 cannot be maintained.

Secondly, there is no suggestion or motivation to combine a muramyl peptide with GM-CSF in Masihi et al. The prior art must suggest the desirability of making a modification in order for the Examiner to make a prima facie case. In re Brouwer, 37 U.S.P.Q.2d 1663 (Fed. Cir. 1995).

When read as a whole, Masihi et al. discloses that muramyl dipeptide (MDP) has some antiviral activity against HIV infection. The conclusions reached in this publication are clearly set forth in the last paragraph at page 397 which states:

> The rational for employing agents with the potential to stimulate endogenous CSF production is the possibility they offer for counteracting bone marrow suppression observed in infections and therapy with certain drugs. Muramyl peptides possessing anti-HIV and CSF induction activities may be useful for balancing bone marrow toxicity observed in individuals being treated with dideoxynucleoside analogs like zidovudine. Future studies involving combination of

> muramyl peptides and dideoxynucleoside analogs are warranted.

Thus, when Masihi et al. is read as a whole it suggests to one skilled artisan to use various muramyl peptides in combination with dideoxynucleoside analogs. It does not suggest, as the Examiner maintains to combine muramyl peptides with GM-CSF.

Indeed, it is clear that the Examiner has applied hindsight reconstruction in rendering this rejection, using the Appellant's patent application as a guide knowing that the specification teaches that the claimed muramyl peptides inhibit immunodeficiency retrovirus replication, like zidovudine.

This is forbidden as stated in In re Pleuddemann, 910 F2d 823, 828, 15 USPQ2d 1738, 1742 (Fed. Cir. 1990) by Federal Circuit:

> It is legal error to use "[an inventor's patent]" specification teaching [of both a novel and nonobvious compound and methods of using that compound] as through it were prior art in order to make claims to [the] methods [of use] appear to be obvious.

See also, In re Gorman, 933 F2d 982, 987, 18USPQ2d 1885, 1888 (Fed. Cir. 1991).

However, Masihi et al. never suggested combining a muramyl peptide with GM-CSF. Indeed, Masihi et al. recognized that although there was some inhibition of HIV-1 using MDP, this inhibition by itself was not sufficient to use MDP alone to treat AIDS. Rather, treatment with a dideoxynucleoside analog was required.

Indeed, the skilled artisan would in fact question this combination, since as stated at page 394 in the paragraph prior to "Materials and Methods" MDP was known to enhance monocyte-macrophage CSF serum. The skilled artisan knowing this fact would not be motivated to use GM-CSF with a MDP that produces CSF or use a "double dosage" of colony stimulating factor to treat AIDS since Masihi et al. clearly indicate the use of muramyl peptide with a dideoxynucleoside analog.

Moreover, there is simply no suggestion or even motivation in Masihi et al. to substitute zidovudine with murabutide and then further combine this particular muramyl peptide with GM-CSF, as required by law when the disclosure of a reference requires that some modification be made.

A case very similar to the present issue is that of In re Kotzab, 217 F.3d 1365, 55 USPQ2d 1313 (Fed. Cir. 2000), in which pieces of a sole prior art reference were

combined. In this case, the Federal Circuit court stated the following:

> [e]ven when obviousness is based on a single prior art reference, there must be showing of a suggestion or motivation to modify the teachings of that reference...Moreover, the test for establishing an implicit teaching, motivation or suggestion is what the combination of these two statements of Evans would have suggested to those of ordinary skill in the art, the two statements cannot be viewed in the abstract. Rather, they must be considered in the context of the teaching of the entire reference. Further, a rejection cannot be predicated on the mere identification in Evans of individual components of claimed limitations. Rather, particular finding must be made as to the reason of the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed.

It should be apparent that the Examiner has not provided any motivation why the skilled artisan would have selected to substitute zidovudine with murabutide and then further combine this particular muramyl peptide with GM-CSF, especially in view of Masihi et al.'s teaching that a dideoxynucleoside analog should be present.

Appellants again submit that this combination was made by the Examiner through hindsight and with the Appellant's claimed invention clear in her mind. This type of analysis is forbidden by law in maintaining an obviousness

rejection. As such, the invention of claims 31-33 is not obvious over Masihi et al.

The required Appeal Brief fee in the amount of $160.00 was previously paid for on January 6, 2003.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

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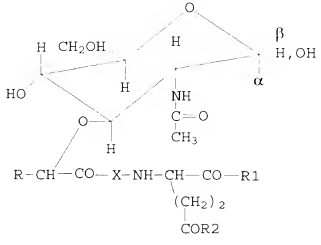
GMM/MAA/
2121-0128P

CLAIMS APPENDIX

25. A process for inhibiting the replication of acquired immunodeficiency retroviruses in man or in those animals which said retroviruses are capable of infecting, which comprises administering as a principal ingredient to said man or said animals in need of such treatment an effective amount of a muramyl peptide of formula:



in which the group R is a methyl group; X is an L-alanyl residue, and R1 is an $O(CH_2)_xH$ group with x= 1, 2, 3 or 4, R2 is, independently of R1, either an amino or an $O(CH_2)_xH$ group with x= 1, 2, 3 or 4, and wherein said effective amount is also an amount that is capable of causing a 100% inhibition of the replication of said retroviruses in primary cultures of monocytes of the host.

26. The process of claim 25, wherein both R1 and R2 are $O(CH_2)_xH$ groups.

28. The process of claim 25, wherein the muramyl peptide is Murabutide.

29. The process of claim 25, which is for the prevention or treatment of AIDS or related syndromes.

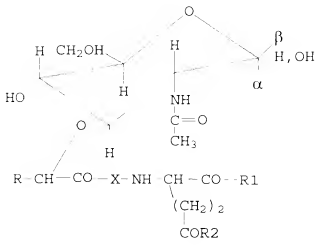
30. The process of claim 25, which comprises administering said muramyl peptide together with another molecule capable of enhancing the anti-retroviral action of said muramyl peptide.

31. The process of claim 30, wherein the other molecule is a cytokine.

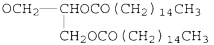
32. The process of claim 30, wherein the other molecule is GM-CSF.

33. The process of claim 30, wherein the other molecule is a protease inhibitor.

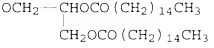
34. The process of claim 25, wherein the muramyl peptide has the formula:



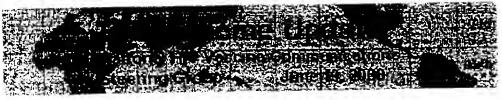
in which the R is methyl; X is an L-alanyl residue or L-threonyl residue, and R1 is an $O(CH_2)_xH$ group with X = 1, 2, 3, or 4, R2 is, independently of R1, either an amino or an $O(CH_2)_xH$ group with X = 1, 2, 3, or 4 or group:



it being understood that, when X is an L-alanyl residue, at least one of these two groups R1 and R2 is an $O(CH_2)_xH$ group as defined above, and that R2 cannot be a group:



and wherein said effective amount is also an amount that is capable of causing a 100% inhibition of the replication of said retroviruses in primary cultures of monocytes of the host.



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